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Gum Arabic Alleviates Aluminum Chloride-Induced Kidney Damage via XRCC1 Upregulation and Ki67/P53 Downregulation

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ABSTRACT

The kidneys are essential for filtering and eliminating waste from the body, but their function can be compromised by oxidative stress caused by reactive oxygen species. This study investigated the protective effects of Gum Arabic (GA), an FDA-approved dietary fiber, against aluminum chloride ($AlCl_3$)-induced kidney injury in rats, focusing on XRCC1 gene expression and Ki67 and p53 immunoreactivity. A total of 20 male Wistar rats were allocated into four groups (n = 20). The control group (group 1) received no treatment. Group 2 was exposed to $AlCl_3$ via intraperitoneal (IP) injection at a dose of 5 mg/kg for two weeks. Group 3 was administered GA extract orally at 500 mg/kg for four weeks. Group 4 was subjected to $AlCl_3$ treatment (5 mg/kg IP) for two weeks, followed by oral administration of GA extract (500 mg/kg) for four weeks. Several parameters were analyzed, including body weight, kidney-to-body weight ratio, serum urea, uric acid levels, oxidative stress markers, XRCC1 gene expression, kidney histology, and Ki67 and p53 immunoreactivity. The results showed that $AlCl_3$ exposure led to a decline in SOD and GSH levels, structural changes in kidney tissue, elevated serum urea, increased lipid peroxidation, and enhanced Ki67 and p53 immunoreactivity. However, post-treatment with GA effectively counteracted these effects. These findings suggest that GA exhibits nephroprotective properties against $AlCl_3$-induced kidney toxicity.

Keywords: Kidney toxicity, Oxidative stress, XRCC1, Ki67, p53, Gum Arabic

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Introduction

The kidneys are vital organs responsible for filtering blood, eliminating metabolic waste, maintaining fluid balance, and producing essential hormones [1-4]. Each kidney contains millions of nephrons, the functional units that facilitate these processes. However, exposure to harmful substances such as drugs, industrial chemicals, and environmental toxins—commonly referred to as nephrotoxicants—can impair kidney function and lead to nephrotoxicity [5, 6]. Several compounds, including aminoglycoside antibiotics, heavy metals (such as lead, mercury, and arsenic), cisplatin, certain fungi, molds, and even recreational drugs like cocaine, have been identified as nephrotoxic [7]. Kidney damage is often assessed using biomarkers such as urine output, glomerular filtration rate, blood urea nitrogen, and serum creatinine. However, some nephrotoxic agents can cause renal injury without significantly affecting these markers, prompting further research into molecular and biochemical mechanisms, oxidative stress-related damage, and cellular transport systems involved in nephrotoxicity [7-10].
Aluminum chloride ($AlCl_3$), a yellow crystalline compound, is widely used in industrial applications, particularly in the production of aluminum. The Agency for Toxic Substances and Disease Registry classifies it as a hazardous substance due to its potential health risks [8]. Human exposure to aluminum occurs through multiple sources, including food (such as cheese, grains, and vegetables), cosmetics, cookware, packaging materials, and water

purification processes [11]. Additionally, aluminum-based compounds, including $AlCl_3$, are utilized in pharmaceuticals for the production of vaccines, injectable allergens, phosphate binders, aspirin, and antacids [11, 12]. The primary entry routes for aluminum into the body are ingestion and inhalation, with excretion occurring mainly through urine. However, excessive accumulation in the kidneys can result in toxicity [11]. Studies have linked $AlCl_3$ exposure to renal tubular degeneration, oxidative stress, and DNA damage due to increased reactive oxygen species (ROS) production and depletion of intracellular glutathione (GSH) [11, 12]. Beyond kidney toxicity, aluminum compounds have also been associated with hepatotoxicity, genotoxicity, microcytic hypochromic anemia, and neurodegenerative conditions such as Alzheimer's disease [12].

Gum Arabic (Acacia gum) is a natural, edible biopolymer derived from the stems of various *Acacia* species, including *Acacia senegal*, *Acacia seyal*, and *Acacia nilotica* [13]. Found primarily in Africa and Asia [14], it has been classified as safe for human consumption by the United States Food and Drug Administration [15]. Its phytochemical composition includes flavonoids, tannins, alkaloids, saponins, carbohydrates, cardiac glycosides, and terpenoids [14]. Gum Arabic (GA) has long been used for medicinal purposes, particularly in renal health. Studies suggest that it aids in improving creatinine clearance, enhancing renal excretion, and reducing plasma urea, phosphate, proteinuria, and glucosuria. Additionally, it has been shown to lower blood pressure and cholesterol levels. Due to its antioxidant properties, GA helps mitigate oxidative stress caused by ROS and has also been used to treat diarrhea [13].

The X-ray repair cross-complementing 1 (XRCC1) gene, located on chromosome 19, encodes a protein responsible for repairing oxidative DNA damage and single-strand breaks caused by alkylating agents and ionizing radiation [16]. Variants in the ERCC1 gene have been associated with alterations in DNA repair pathways, which may influence kidney recovery following injury [17, 18]. Research suggests that nucleotide excision repair genes are involved in removing DNA lesions and play a role in renal cellular responses to cisplatin-induced nephrotoxicity [19].

This study aims to evaluate the nephrotoxic effects of $AlCl_3$ in rats and investigate its impact on the DNA repair mechanisms mediated by XRCC1. Additionally, we examine the potential protective role of GA in alleviating $AlCl_3$-induced kidney damage and explore its underlying mechanisms of action.

Materials and Methods

Plant material

GA was sourced from a herbal and traditional medicine market in Saudi Arabia. The collected material was finely ground using a blender. To prepare the extract, 10 grams of the powdered GA were dissolved in 100 milliliters of distilled water. The solution underwent filtration and was concentrated to achieve a final extract concentration of 8.5 mg/ml. It was then stored at 4 °C until required for experimental use.

Animals

Male Wistar rats, each weighing between 150 to 250 grams, were obtained from the King Fahd Medical Research Center at King Abdulaziz University in Jeddah, Saudi Arabia. The animals were kept in a controlled environment with a 12-hour light/dark cycle and were provided with unrestricted access to food and water. To ensure adaptation to their surroundings, they were maintained under these conditions for one week before the experiment commenced. Ethical approval for the study was granted by the Animal Ethics Committee of King Abdulaziz University's College of Medicine.

Chemicals

Aluminum chloride ($AlCl_3$) used in this study was purchased from Sigma-Aldrich, USA. All other chemicals used were of the highest purity available.

Experimental design

Following the acclimatization period, the rats were randomly assigned to four experimental groups, each consisting of five animals. The first group served as the untreated control. The second group received an intraperitoneal injection of $AlCl_3$ at a dose of 5 mg/kg body weight daily for two weeks. In the third group, animals were administered an oral dose of GA extract at 500 mg/kg body weight daily for four weeks. The fourth group

initially received the same $AlCl_3$ intraperitoneal dosage as the second group for two weeks, after which they were given GA extract orally at 500 mg/kg body weight for four additional weeks.

After the experimental period, the animals were fasted overnight before being euthanized under diethyl ether anesthesia. Kidney tissues were surgically removed, rinsed with normal saline, and weighed. Blood samples were collected from the abdominal aorta. Some portions of the kidney tissue were stored at -80 °C for RNA extraction, while others were preserved in 10% buffered formalin for histological and immunohistochemical analyses. The remaining kidney samples were homogenized in 100 mM phosphate buffer (pH = 7.4) at 14,000 rpm for 30 minutes.

Quantification of serum kidney function biomarkers

To assess kidney function, serum levels of urea and uric acid were determined using a commercial assay kit from Diagnostic System Laboratories Inc., USA, following the manufacturer's instructions.

Evaluation of antioxidant enzymes in kidney tissue

The levels of key antioxidant enzymes in kidney tissue were analyzed using the liquid fraction obtained after centrifugation. A commercial assay kit from MyBioSource was employed to measure the activity of catalase (CAT) and superoxide dismutase (SOD), following the manufacturer's specified procedures.

Determination of glutathione and lipid peroxidation markers

To assess oxidative stress within the kidney tissue, the concentrations of glutathione (GSH) and malondialdehyde (MDA) were determined. These biomarkers were quantified using a MyBioSource commercial kit (California, USA). The analysis was carried out using the supernatant obtained after centrifugation at 14,000 rpm, following the kit's guidelines.

Isolation of RNA and quantitative real-time PCR (RT-qPCR) analysis

Total RNA was extracted from kidney tissue samples utilizing the QIAgen RNeasy Mini Kit (cat #74104), strictly adhering to the manufacturer's protocol. Complementary DNA (cDNA) synthesis was performed using 200 ng of the extracted RNA with the M-MLV Reverse Transcriptase System. The qPCR reaction mixture was prepared by combining 3 µL of cDNA, 0.5 µL of both forward and reverse primers (500 nM each), 1 µL of nuclease-free water, and 3 µL of SYBR Green Master Mix. The primer sequences utilized in the study are provided in **Table 1**. Gene expression levels were quantified using the $2^{-\Delta\Delta CT}$ method, with GAPDH serving as the internal reference for normalization.

Table 1. Primer sequences

Primers	Primers sequence (5`-3`)
XRCC1 - left	5'-TTCACAGCCCTCCAGACAAAG-3'
XRCC1 right	5'-CGGAACTGGCCGAGCTT-3'
GAPDH - left	5'-GAT GGT GAA GGT CGG TGT G-3'
GAPDH -right	5'-ATG AAG GGG TCG TTG ATG G-3'

Histopathological examination

The kidney samples were preserved in 10% buffered formalin, followed by embedding in paraffin wax after dehydration in a graded ethanol series at room temperature for one day. To investigate histopathological alterations, thin sections from the tissue blocks were stained using hematoxylin and eosin (H&E). Microscopic images of the stained kidney sections were captured at a magnification of 400x for analysis.

Immunohistochemical analysis

Immunohistochemistry was performed to detect Ki67 and p53 proteins using a streptavidin-biotin method. The kidney tissue sections (5 µm) were first deparaffinized and incubated with a 0.3% hydrogen peroxide solution in methanol for 30 minutes to inhibit endogenous peroxidase activity. Following this, the sections were incubated with anti-Ki67 and anti-p53 antibodies at a dilution of 1:100, with subsequent counterstaining using hematoxylin and eosin.

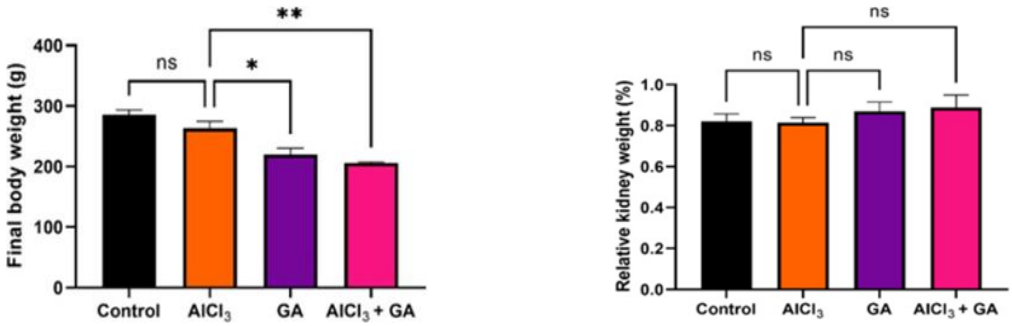
Statistical approach

Data were analyzed using one-way ANOVA, with results presented as mean ± standard error of the mean (SEM). Dunnett's multiple comparisons test was applied to compare means between groups, and a p-value of less than 0.05 was considered statistically significant.

Results and Discussion

Impact of AlCl3 and GA on body and kidney weights

AlCl3 is known to be a toxic substance, and in this study, we investigated its effects alongside the potential protective role of GA on body weight and relative kidney weight in rats. The results showed that exposure to AlCl3 did not lead to any significant change in the body weight of rats when compared to the control group **(Figure 1a)**. However, rats treated with GA exhibited a significant ($P < 0.05$) change in body weight. Furthermore, when GA was administered after AlCl3 exposure, the body weight of these rats was significantly lower ($P < 0.01$) than that of the group treated with AlCl3 alone **(Figure 1a)**. Regarding relative kidney weight, no notable differences were observed among the groups **(Figure 1b)**.

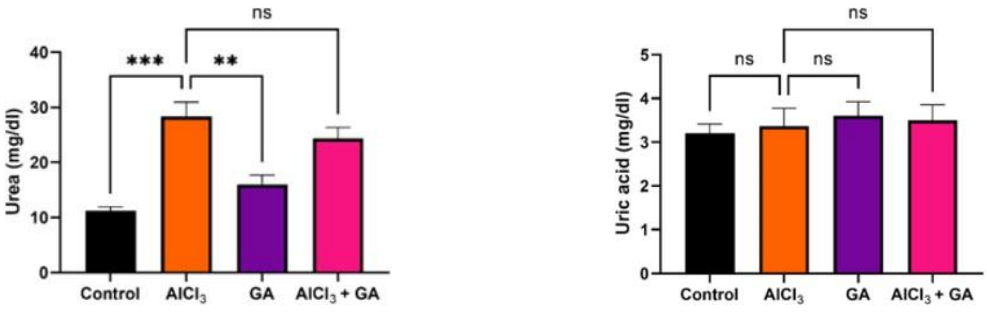


a) b)

Figure 1. Effects of AlCl3 and GA on the final body weight and relative kidney weight; a) final body weight, and b) relative kidney weight

Effects of GA and AlCl3 on serum kidney biomarkers

This study further examined how AlCl3 and GA influenced two key serum markers for kidney function: uric acid and urea. The data showed that AlCl3-treated rats exhibited significantly higher serum urea levels compared to the control group ($P < 0.001$). In contrast, the rats that received only GA demonstrated a significant reduction ($P < 0.01$) in urea concentration compared to the AlCl3 group **(Figure 2a)**. Additionally, while the reduction in serum urea levels was not statistically significant in the group treated with AlCl3 followed by GA, there was a 14% decrease in urea levels compared to those exposed solely to AlCl3 **(Figure 2a)**. However, serum uric acid levels remained essentially unchanged across all experimental groups **(Figure 2b)**.



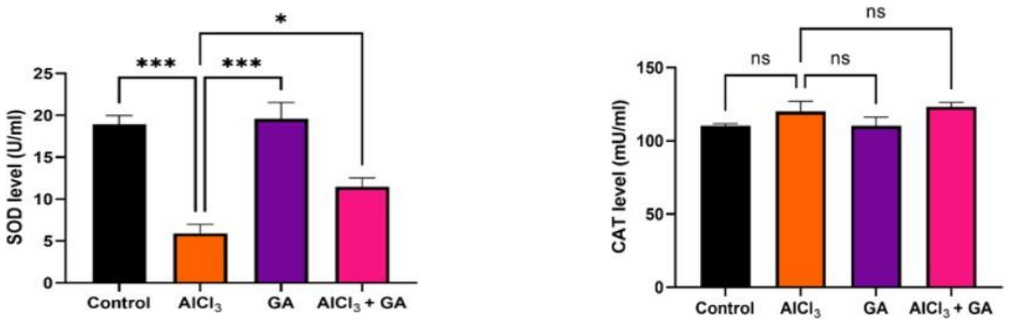
a) b)

Figure 2. Effects of AlCl3 and GA on serum kidney function biomarkers; a) urea, and b) uric acid

Impact of GA and AlCl3 on kidney tissue antioxidant activity

The activity of key antioxidant enzymes, catalase (CAT) and superoxide dismutase (SOD), in the kidneys was assessed in this study to explore the effects of AlCl3 and GA. As expected, the results shown in **Figure 3a** indicate

that AlCl3-treated rats had significantly reduced SOD activity compared to both the control group and the GA-only treated group ($P < 0.001$). Notably, when GA was administered after AlCl3 treatment, there was a significant increase in SOD activity compared to the group treated with only AlCl3 **(Figure 3a)**. In contrast, catalase activity was consistent across all experimental groups, with no significant differences observed **(Figure 3b)**.

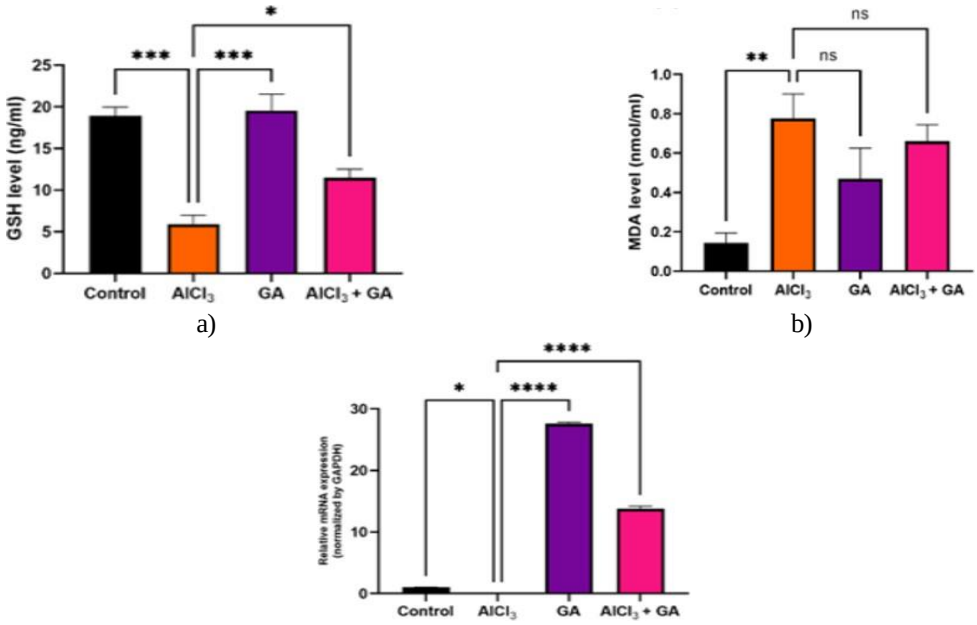


a) b)

Figure 3. Effects of AlCl3 and GA on kidney tissue antioxidant level; a) superoxide dismutase, and b) catalase

Effects of AlCl3 and GA on tissue GSH, MDA Levels, and XRCC1 gene expression

This study next investigated how AlCl3 and GA influenced antioxidant levels in tissue, along with the expression of the XRCC1 gene. The results indicated that AlCl3-treated rats exhibited significantly lower GSH levels in their kidneys compared to both the untreated control group and the rats treated only with GA ($P < 0.001$) **(Figure 4a)**. Additionally, when GA was administered after AlCl3 exposure, there was a marked increase in kidney GSH concentrations relative to the AlCl3-only treated group. Regarding malondialdehyde (MDA) levels, a noticeable increase ($P < 0.01$) was observed in rats treated with AlCl3 when compared to the untreated control group **(Figure 4b)**. Rats treated with GA alone, as well as those who received GA after AlCl3 treatment, showed reductions of 39% and 15%, respectively, in MDA levels compared to the AlCl3-only group. Furthermore, AlCl3 administration led to a significant decrease in XRCC1 gene expression when compared to the control group ($P < 0.005$) and the GA-only treated rats ($P < 0.0001$) **(Figure 4c)**. Remarkably, when GA was given after AlCl3 treatment, there was a substantial increase in XRCC1 gene expression compared to the AlCl3-only group **(Figure 4c)**.



a) b)

c)

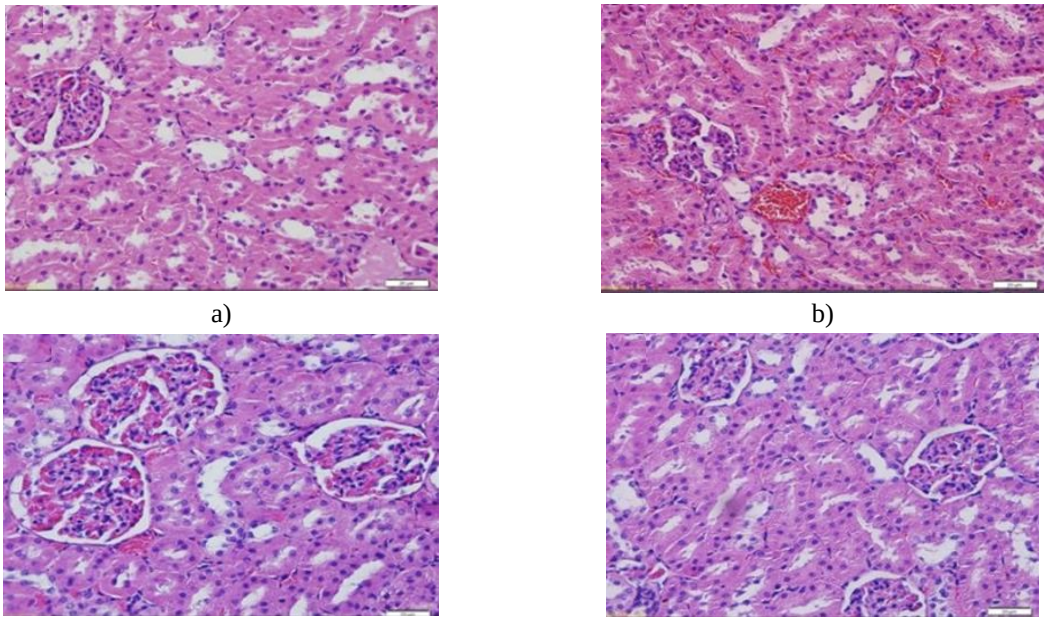
Figure 4. Effects of AlCl3 and GA on tissue GSH and MDA levels and the expression of XRCC1 gene; a) tissue glutathione (GSH) level, b) tissue malondialdehyde (MDA) level, and c) relative XRCC1 gene expression

Impact of AlCl3 and GA on kidney histology

This study assessed how AlCl3 injection and GA treatment influenced the histological structure of the kidneys. As illustrated in **Figure 5**, the kidney tissue from both the control and GA-treated groups exhibited normal architecture, with no visible structural changes or macrophage infiltration **(Figures 5a and 5c)**. In contrast, the kidneys of rats administered AlCl3 exhibited mild necrosis, characterized by an expanded Bowman's space, degeneration of the glomerular capillaries, infiltration, macrophage, and thickening of the outer renal membrane **(Figure 5b)**. Notably, treatment with GA following AlCl3 exposure alleviated these histological alterations, restoring the kidney structure to normal **(Figure 5d)**.

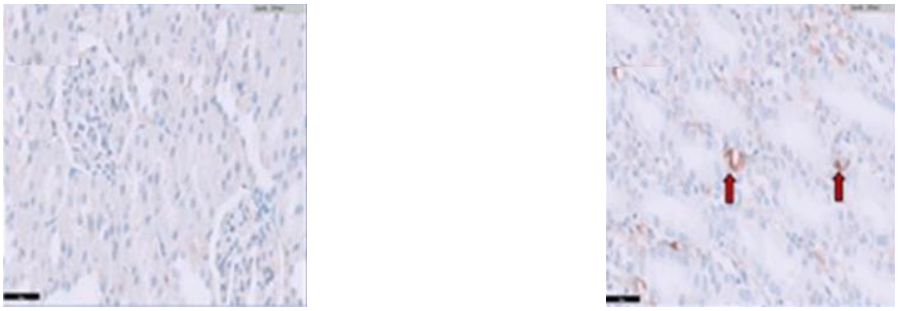
Effects of AlCl3 and GA on Ki67 and p53 immunoreactivity

In the final part of the study, the effects of AlCl3 and GA treatment on the immunoreactivity of proliferation and apoptosis markers, Ki67 and p53, were examined. AlCl3 administration led to a significant increase in the number of brown-staining cells positive for Ki67 and p53 in the kidneys **(Figures 6b and 6c)**. On the other hand, kidneys from both the control group and GA-only treated rats showed no reactivity to these markers. Interestingly, rats treated with GA after AlCl3 exposure showed a marked reduction in immunostaining for both Ki67 and p53, compared to those treated with AlCl3 alone **(Figures 6d and 6h)**. This suggests that GA treatment may reduce both cell proliferation and apoptosis in the kidneys.



a) b) c) d)

Figure 5. Impact of AlCl3 and GA on kidney histology; a) The kidney histology from the control group displayed normal renal structure, b) the kidneys of rats treated with AlCl3 showed mild necrosis and infiltration of macrophages, c) the kidney histology of the group treated with only GA exhibited normal tissue structure, and d) rats treated with both AlCl3 and GA displayed improved renal histology, with the tissue returning to normal appearance.



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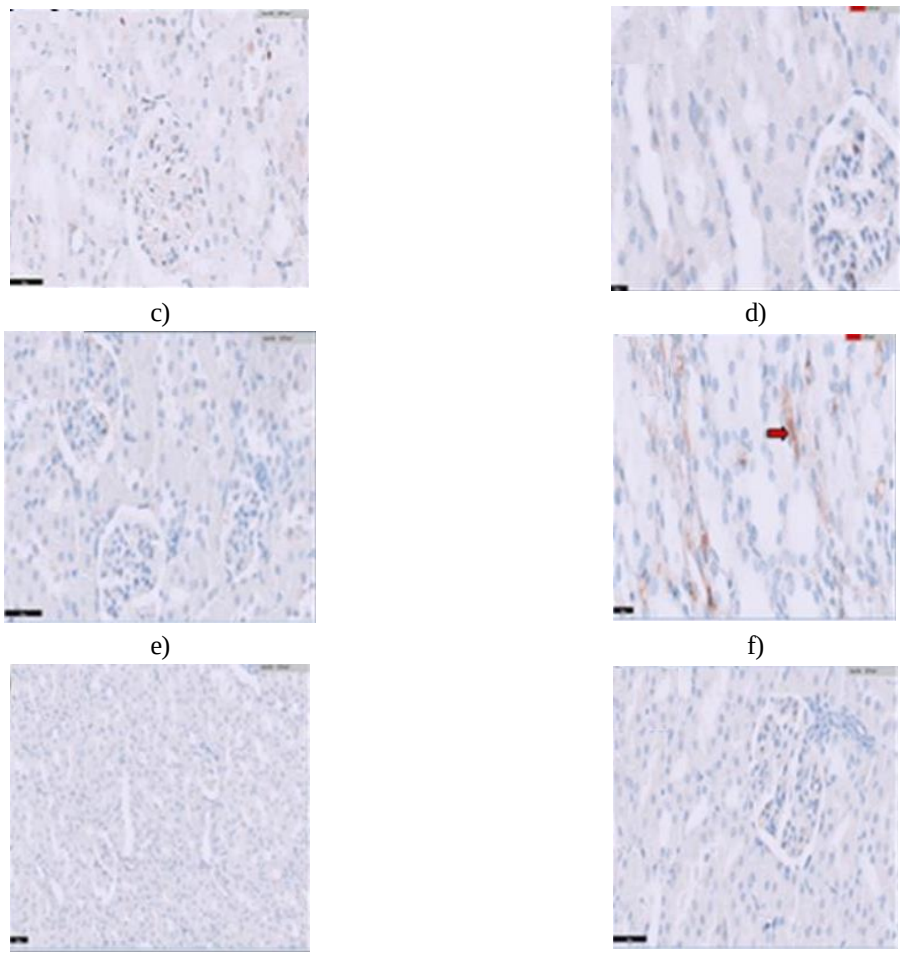

Figure 6. Immunoreactivity of Ki67 and p53 in response to AlCl3 and GA; a) immunohistochemical staining for Ki67 in the kidney sections of the control group revealed no positive reactivity, b) immunohistochemical staining for Ki67 in the kidneys of AlCl3-treated rats showed significant positive reactivity, c) the kidneys of rats treated with GA alone showed no Ki67 reactivity, d) the combination of AlCl3 and GA resulted in negative reactivity for Ki67 in the kidneys, e) immunostaining for p53 in kidney sections from the control group showed no reactivity, f) AlCl3 treatment induced positive reactivity for p53 in the kidney sections, g) No p53 immunoreactivity was observed in the GA-only group, and h) the group treated with both AlCl3 and GA exhibited negative reactivity for p53.

The kidneys are vital in excreting aluminum (Al) and its compounds, such as AlCl3, making them susceptible to toxicity due to the retention of these substances. Aluminum is eliminated through various mechanisms in the kidneys, including tubular reabsorption, glomerular filtration, and secretion in the distal tubules [12]. This study investigates the protective effects of GA on AlCl3-induced kidney damage. The findings show that AlCl3 did not affect the body or kidney weights in the treated rats compared to the control group, which aligns with a similar study by Belaïd-Nouira *et al*. [20] However, GA treatment significantly reduced the animals' body weight, especially in rats previously exposed to AlCl3, possibly due to its role as a dietary fiber, which helps improve fat metabolism and induce satiety [21].

Serum urea and uric acid levels were evaluated as indicators of kidney damage. Urea, a nitrogenous byproduct of amino acid metabolism, is filtered by the glomeruli and reabsorbed by renal tubules before being excreted [22]. Uric acid, a product of purine metabolism, is produced mainly in the liver, kidneys, and intestines [23]. High concentrations of either marker signal kidney damage [22, 24]. In our study, AlCl3 treatment significantly raised serum urea levels, but GA administration reduced them by 14%. In contrast, serum uric acid levels remained unchanged across all groups, corroborating findings by Al-Kahtani [25]. His study also reported an increase in urea, though the change in uric acid levels was not significant.

To assess kidney function further, antioxidant levels were measured, as oxidative stress is a major cause of kidney damage. We focused on the enzymes superoxide dismutase (SOD) and catalase (CAT), and the biomarkers glutathione (GSH) and malondialdehyde (MDA). SOD and CAT are essential antioxidants that protect against reactive oxygen species (ROS), and reduced SOD activity has been linked to kidney dysfunction [26]. Our results showed that AlCl3 significantly decreased SOD activity, consistent with previous studies by Al-Kahtani [25] and Al Dera [12]. However, when GA was administered, it reversed the SOD reduction caused by AlCl3. On the other hand, no significant changes in CAT activity were observed, possibly due to the short treatment duration in this study.

AlCl3 also depleted kidney GSH and increased MDA levels, both indicators of oxidative stress. GSH is critical for protecting against ROS-induced damage, including DNA damage, while elevated MDA suggests lipid peroxidation in kidney tissue [27, 28]. GA administration significantly reversed these changes, aligning with findings from Al Dera [12], Othman *et al.* [29], and Ahmed *et al.* [30]. These results further support GA's antioxidant capabilities, as documented in earlier research [27, 31].

The X-ray repair cross-complementing 1 (XRCC1) gene plays a vital role in DNA repair, particularly in repairing single-strand breaks. A reduction in the expression of DNA repair genes has been linked to kidney diseases [32]. In this study, AlCl3 treatment resulted in significant downregulation of XRCC1, causing oxidative DNA damage [33]. However, GA administration led to the upregulation of XRCC1 expression, demonstrating its potential to counteract DNA damage and enhance DNA repair.

Histological analysis of the kidneys revealed that AlCl3 treatment caused necrosis, glomerular capillary degeneration, macrophage infiltration, and thickening of the outer kidney membrane. These findings are consistent with studies by Al-Kahtani [25] and Al Dera [12] on AlCl3-induced kidney damage. Interestingly, GA treatment reversed these structural changes, highlighting its nephroprotective effects.

The study also examined Ki67 and p53, markers of cell proliferation and apoptosis, respectively. Ki67 is a nuclear protein associated with cell division, while p53 induces apoptosis in response to DNA damage [34-38]. AlCl3 treatment led to increased expression of both markers in kidney cells, indicating that AlCl3 may induce proliferation and apoptosis, potentially contributing to renal cancer. However, GA administration attenuated the expression of both Ki67 and p53, suggesting that GA has the potential to reduce kidney cell proliferation and apoptosis induced by AlCl3 toxicity.

Conclusion

In this study, the nephroprotective potential of GA against AlCl3-induced toxicity in rats and its effect on the expression of the XRCC1 gene were evaluated. The findings indicated that AlCl3 treatment did not cause significant changes in the body or kidney weights of the rats. However, AlCl3 exposure led to a decrease in kidney superoxide dismutase (SOD) and glutathione (GSH) levels, as well as disruptions in kidney tissue structure, along with increased serum urea levels, higher lipid peroxidation, and enhanced immunoreactivity for Ki67 and p53. Remarkably, after GA administration following AlCl3 exposure, rats showed an increase in SOD activity, higher GSH levels, reduced urea, and lipid peroxidation, elevated XRCC1 gene expression, and a decrease in Ki67 and p53 immunoreactivity. These results suggest that GA holds promise as a nephroprotective agent in counteracting AlCl3-induced nephrotoxicity.

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Conflict of Interest: None

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Ethics Statement: None

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